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Treatment of an Acquired Coagulopathy with Recombinant Activated Factor VII in a Damage-Control Patient

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Recombinant activated factor VII is commonly used for the treatment of hemophiliac patients with inhibitors and has been studied for use in trauma. We report the use of recombinant activated factor VII for a male patient who was injured in a motor vehicle accident. We also summarize the animal studies and clinical trials that have been reported.

Introduction

Recombinant activated factor VII (rFVIIa) is a Food and Drug Administration-licensed drug that has been approved and is commonly used for the treatment of hemophiliac patients with inhibitors.[1-4] Interest in the drug's blood-clotting abilities have led to studies in normal animals to evaluate its effects on blood loss, blood pressure, and survival rates in models of acquired coagulopathy and severe trauma.[5-10] To date, only one prospective randomized study has documented rFVIIa use for elective surgery but results were encouraging, with reduced blood loss and decreased transfusion after a single preoperative dose.[11] In addition, a growing body of literature continues to catalog the successful use of rFVIIa in surgery and for patients with the acquired coagulopathy of trauma.[11-13] In our own experience, a case recently treated at our urban, level 1 trauma center also demonstrates the potential usefulness of this drug.

Case Report

A 17-year-old male patient was ejected from a motor vehicle while street racing. The emergency medical service reported multiple deaths at the scene. On emergency medical service arrival, the patient's systolic blood pressure was 96 mm Hg (by palpation), pulse was 120 beats/min, and Glasgow Coma Scale score was 12. He was transported via helicopter and presented in the emergency center as hypotensive (85/46 mm Hg) and tachycardic (130 beats/min), with a distended abdomen and a midhumeral amputation of his left arm. C-spine and pelvis plain films were normal, whereas a chest radiograph documented significant bilateral pulmonary contusions. A pneumatic tourniquet was placed proximally on his left arm. His abdominal ultrasound revealed free fluid in the pelvis and left upper quadrant. Resuscitation was begun with both crystalloid and O negative packed red blood cells (PRBCs), and the patient was moved expeditiously to the operating room. On arrival in the operating room, the patient had arterial blood gas values of pH 6.94, carbon dioxide pressure of 59 mm Hg, oxygen pressure of 68 mm Hg, bicarbonate level of 13.7 mmol/L, and base excess of −19 mmol/L.

On abdominal entry, significant hemoperitoneum was encountered. Examination of the spleen revealed a grade IV laceration with active bleeding, necessitating a splenectomy. The pelvic contents, small intestine, and colon were found to be free of injury. An expanding, left lateral, retroperitoneal hematoma was noted. After appropriate exposure and proximal vascular control, bleeding from the left renal hilar region was discovered, necessitating a left nephrectomy. During the operation, the patient became difficult to ventilate; bilateral thoracostomy tubes were placed and ventilation improved. The patient subsequently became hypothermic and coagulopathic, which necessitated packing of the left upper quadrant and retroperitoneum with gauze sponges and temporary abdominal closure with a Bogotá bag. By the end of the procedure, the patient had received a total of 24 units of PRBCs, 4 units of fresh frozen plasma, and 6 units of platelets. The patient was transferred to the shock trauma surgical intensive care unit.

On arrival in the shock trauma surgical intensive care unit, the patient was hypoxic because of bilateral pulmonary contusions and was therefore placed on a high-frequency oscillatory mode of ventilation, which improved his arterial blood gas values (pH 7.34; carbon dioxide pressure, 37 mm Hg; oxygen pressure, 83 mm Hg; bicarbonate level, 20 mmol/L; base excess, −5 mmol/L; fraction of inspired oxygen, 100%). His hemoglobin and hematocrit levels were 13.0 g/dL and 33.4%, respectively, with a platelet count of 52,000 platelets/μL, prothrombin time of 20.4 seconds, activated prothrombin time of 53.2 seconds, and fibrinogen level of 119 mg/dL. Two units of fresh frozen plasma and 6 units of platelets were administered, and warming measures were continued because the patient's temperature was 33.3°C. Because of the patient's significant hypothermia and coagulopathy, the decision was made to give 90 μg/kg rFVIIa. Two doses of 6,300 μg each were given, at 3 and 7 hours postoperatively. After the patient received the two doses of rFVIIa, the attending trauma surgeon thought that the coagulopathy was corrected and the laboratory data correlated with the clinical impression (Table I).

After 36 hours in the hospital, the patient required no more fresh frozen plasma or platelets and only 2 more units of PRBCs. On hospital day 3, the patient was taken to the operating room for abdominal irrigation, placement of a jejunostomy feeding tube, primary abdominal closure, and washout of his amputa-

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TABLE I

TEMPERATURE, LABORATORY, AND TRANSFUSION DATA BEFORE AND AFTER TWO DOSES OF RFVIIA

	Emergency Center	Before rFVIIa	After 1st rFVIIa	After 2nd rFVIIa	30 Hours after Admission
Temperature	N/A	33°C	34°C	35°C	38°C
PT/PTT (seconds)	14.7/33.7	20.4/53.2	10.7/39.5	9.8/90	12.4/14.1
Hemoglobin (g/dL)	10.5	13.0	11.6	13.7	9.1
Platelets ($10^5/\mu L$)	394	52	109	114	81
Fibrinogen (mg/dL)	N/A	119	156	193	247
PRBC (units)	0	22	0	0	2
FFP (units)	0	6	0	0	2
Platelets (units)	0	16	0	0	6
Fluids (mL)	850	12,000	N/A	N/A	5,000
pH	6.97	7.34		7.37	7.37
BE (mmol/L)	−25	−5		−4	−1

N/A, not available; FFP, fresh frozen plasma; fluids, crystalloid given; BE, base excess; PT, prothrombin time; PTT, partial thromboplastin time.

tion site. On hospital day 4, the patient was changed to a bilevel pressure mode of ventilation. He was taken to the operating room again on days 6 and 10 for debridement and revision of his amputated arm. After the last surgical procedure and 11 days of ventilation support, the patient was extubated and transferred to an intermediate surgical care unit. On hospital day 17, the patient was transferred to an acute rehabilitation facility. He was tolerating a regular diet and required no supplemental oxygen.

Discussion

The patient described had a traumatic amputation of his arm, suffered bilateral pulmonary contusions, was hypotensive and acidotic in the field and in the emergency center, underwent massive resuscitation and transfusion, and became hypothermic and coagulopathic, for which he underwent abdominal damage-control maneuvers. Until the injection of rFVIIa, he demonstrated a classic systemic response to severe injury and subsequent treatment. Mortality rates for trauma patients in this category of injury range between 40% and 50%, and early death is almost always the result of uncontrolled hemorrhage.[12-16] Patients with isolated systolic hypotension (<90 mm Hg) have demonstrated up to 54% mortality rates,[17] and 50% require an urgent operation to control hemorrhage.[18] Sixty-five percent of deaths occur after admission to the hospital, and exsanguination is responsible for between 15% and 40% of hospital deaths among trauma patients.[19] Patients who acutely received >20 units of PRBCs demonstrated a mortality rate of 50%.[15] In addition to uncontrolled bleeding, uncontrolled hypothermia secondary to hemorrhagic shock is an independent risk factor for death.[20] Hypothermia has been shown to be the most predictive element of the systemic inflammatory response syndrome criteria for the development of multiple-organ dysfunction syndrome.[21] A decrease in core temperature frequently coexists with and compounds massive hemorrhage. Hypothermia perpetuates coagulopathic bleeding, and rewarming may take several hours. Acidosis also contributes to coagulopathy and is difficult to reverse while patients are still bleeding.[22] In addition, dilution of clotting factors occurs with massive transfusion, compounding the acquired coagulopathy. The combination of hypothermia, coagulopathy, and acidosis is a self-perpetuating vicious cycle that is rapidly fatal unless interrupted.[12] New methods of hemorrhage control may serve to ameliorate some of these complications.[23] In addition to standard rewarming and blood product replacement, rapid treatment of acquired coagulopathy after severe trauma may be enhanced with injectable drug therapy, such as rFVIIa.

When bound to exposed tissue factor (TF), normally expressed factor VII activates the extrinsic clotting system at the site of injury, without causing systemic hypercoagulability. rFVIIa is an attractive therapy candidate for coagulopathy because it bypasses much of the intrinsic coagulation system, is active only in the presence of exposed TF, and has a rapid onset and a short half-life.[3] TF is not normally expressed in the intact vascular space but exists at high concentrations in the medium and is exposed after vessel injury. TF can be expressed on the surface of activated monocytes after sepsis; however, the significance of this is unclear, because the activity of activated TF (the biologically functional form of the molecule) has not been measured.[24] An alternative hypothesis is that rFVIIa acts by binding to activated platelets and activating factor Xa on the platelet surface, independent of the usual TF cofactor.[25]

An increasing number of published case reports document the use of rFVIIa among patients with acquired coagulopathy from a variety of conditions, i.e., trauma,[26-31] head injury,[32,33] cirrhosis,[34] bone marrow transplant,[35] gastrointestinal bleeding,[36] heart valve replacement,[37] sepsis-induced disseminated intravascular coagulation,[38,39] liver transplant,[40] necrotizing pancreatitis,[41] pulmonary alveolar hemorrhage,[42] and coronary artery bypass.[43] These case reports documented varying levels of effectiveness, and none reported any adverse outcomes directly attributable to the drug. Patients who initially survive massive hemorrhage and sepsis may ultimately succumb to multiple-organ failure.[44] Hardaway and others[45-48] described the possible relationship between diffuse microthrombi and organ failure. It is theoretically possible that modulation of the coagulation cascade by rFVIIa to improve local hemostasis could result in an increased incidence of late multiple-organ failure because of increased microthrombus formation and fibrin deposition. However, during 13 years of clinical use, rFVIIa has produced few cases of myocardial infarction or stroke, which supports the claim that the number of thromboembolic events has been limited despite the widespread use of the drug.[49-52]

Similarly, none of the controlled animal trauma studies that have focused on the hemorrhage-control aspects of rFVIIa have documented any evidence of increased thrombosis or other thrombus-related complications.

Six animal studies evaluated the role of rFVIIa as a hemostatic agent in previously normal animals with severe injuries.[5-10,53] These studies evaluated different combinations of liver and aortic injuries, resuscitation strategies, and dose regimens. Three studies explored rFVIIa as the sole hemostatic agent in warm, coagulation-intact animals.[7,9,10] One of these experiments demonstrated decreased blood loss and improved survival rates,[9] whereas another showed preserved blood pressure.[7] The third study showed no difference in either blood pressure or blood loss.[10] The first two studies suggested that rFVIIa may reduce blood loss sufficiently enough to be considered as a single therapeutic agent in hemorrhage control. Combining the drug with conventional damage-control methods has been a major focus of preclinical research. Along this line, two studies were completed in cold and dilutionally coagulopathic animals with liver injuries.[5,6] rFVIIa was used as an adjunct to gauze packing, in much the same way as described in the current human case report. These two animal studies demonstrated a 46% decrease in blood loss in the rFVIIa-treated animals. Finally, a study using an aortic injury model documented rebleeding at increased mean arterial pressure after injection of rFVIIa, indicating stronger clot formation.[8] None of the animals in any of the six studies demonstrated evidence of thrombotic complications.

Kenet et al.[26] described the first use of rFVIIa for a trauma patient in 1999. The patient was a young soldier with a gunshot wound to the abdomen, which injured, among other structures, the inferior vena cava. rFVIIa was given in a desperate attempt to control the massive coagulopathic bleeding. The intervention was successful, and the patient ultimately survived. In 2002, O'Neill et al.[28] described the first known use of rFVIIa for trauma in the United States. Their patient suffered numerous stab wounds and, despite heroic efforts consisting of three operative explorations and two angiographic embolizations, the patient continued to bleed 45 hours after injury. After administration of 105 units of PRBCs, 90 μg/kg rFVIIa was administered. The patient stopped bleeding immediately but ultimately died of sepsis 5 weeks after injury. An autopsy revealed no evidence of thrombi.

As we describe in this case report, the use of rFVIIa as an adjunct to standard hemostatic maneuvers for the treatment of trauma patients in a damage-control mode is no longer unusual. Many institutions, including our own, have instituted rFVIIa clinical practice guidelines to manage this new therapy to decrease blood loss and transfusion requirements. Martinowitz et al.[27] recently published a report of their first seven trauma patients to receive rFVIIa. At the 2003 American Association for the Surgery of Trauma meeting, Dutton et al.[31] reported favorable results with rFVIIa from their consecutive case series of 52 severely injured trauma patients. In 2004, Dutton et al.[31] reported the reversal of coagulopathy in 61 of 81 coagulopathic trauma patients who were treated with rVIIa.

In what may be seen as a landmark article, Friederich et al.[54] recently reported their successful experience in the first prospective randomized trial of the use of rFVIIa among radical prostate surgical patients. A placebo treatment group was compared with two treatment groups (treated with either 20 or 40 μg/kg rFVIIa). Blood loss was decreased in the rFVIIa groups ($p < 0.01$), whereas transfusions were eliminated in the higher-dose group. Operative time decreased in the rFVIIa group (120 vs. 180 minutes, $p < 0.05$). No deleterious safety issues were identified, and the group of older, procoagulant, male patients who received rFVIIa did not manifest complications associated with hypercoagulopathy. Importantly, Boffart et al.[56] recently reported no safety issues with rFVIIa in a large, prospective, randomized study of severely injured, massively transfused, trauma patients, whereas transfusions were decreased among the blunt-injured patients.

Conclusions

Since 1999, a growing number of human case reports have described the potential usefulness of rFVIIa for patients with acquired coagulopathies resulting from blunt or penetrating injuries. rFVIIa has been shown to decrease blood loss and transfusion requirements among trauma patients with life-threatening hemorrhage, including patients with hypothermia (30–33°C). None of the experienced trauma surgeons reporting these cases described unusual adverse events. A recent prospective study of elective surgery documented decreased blood loss and transfusions, without increased thrombotic complications. In addition, six large, animal, trauma studies have been performed, with no apparent evidence of systemic microthrombi. A prospective, randomized, placebo-controlled, trauma trial has just been completed in 18 countries outside the United States. rFVIIa will no doubt be increasingly used for patients who manifest an acquired coagulopathy. New prospective, randomized, blinded, human trials are required to definitively answer the provocative questions raised by the growing number of studies of acquired coagulopathy treated with rFVIIa.

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